more. One area deserving consideration is the importance of random events in generating cell behavior.

All biological processes, at the cellular as well as the organismal and evolutionary levels, rely on the energy-dependent reinforcement and perpetuation of random accidents to maintain and transmit information. We appreciate the overwhelming importance of random events in evolution, but randomness rules biology at the microscopic level as well. To give one example, the first event in frog development is a random collision between sperm and egg. The arbitrary choice of sperm entry point then determines the direction of the first cortical rotation and, in direct consequence, the primary body axis of the tadpole. If the direction of the cortical rotation is experimentally altered, a normal tadpole still develops but with its body axis defined by the artificial rotation [3]. No level of detail in understanding the chemistry of the egg could enable us to calculate exactly how it will develop without this absolutely critical random input. How can frog eggs accept random initial axial determinants but all generate tadpoles that look more or less alike?

This property of living systems — the capacity for plucking order and reproducibility out of random chaos — is not unique to the egg. In many developing tissues, if a particular cell is destroyed, one of its neighbors will assume its fate. The differing fates of individual cells within an 'equivalence group' of cells with the same set of potential fates may be determined by signals arising either from outside the group (induction) or from other cells within the group (lateral specification or lateral inhibition) [4]. In vertebrates, invertebrates, and even cooperative colonies of free-living amoebae, lateral specification often occurs when one cell in the equivalence group, apparently at random, gains a slight lead on its fellows in the race towards a chosen fate. The winning cell then sends signals to the other members of the equivalence group to prevent them from assuming the same fate, or to direct them to assume an alternative fate. In most cases, it cannot be predicted and does not seem to matter which cell in an equivalence group wins the race. Each embryo becomes a functional adult, regardless of the precise origin and history of any given cell.

We can predict that the explanations for these amazing feats must lie in the spectacularly wasteful expense of energy by living cells. Living systems are always in a state very far from chemical equilibrium, but not all non-equilibrium states are equally likely, and very few of them are conducive to the perpetuation of life. How particular non-equilibrium states are assiduously pursued by every cell, and how every cell maintains its profound metastability and remains poised to follow an effectively infinite variety of behaviors, remain fundamental mysteries. Cells do not disobey the laws of thermodynamics, but rather hydrolyze enormous quantities of ATP in a highly directed way in order to defy them. Thus, we can expect that one particularly important principle in cell biology will be defined when my question for Wolpert's "good fairy godmother of science" has been answered: how exactly does the cell trade off energy consumption against the normal effects of entropy, so that it can exploit random events in such a way as to yield consistent, predictable behavior? Once we know this, we may begin to answer arguably the most fundamental question in biology: what exactly is the difference between living and non-living chemical systems?

References

1. *Quoted in* Crease RP, Mann CC: *The Second Creation: Makers of the Revolution in Twentieth-Century Physics*. New York: Macmillan Publishing; 1986:10.
2. Wolpert L: The good fairy godmother of science. *Curr Biol* 1996, 6:2.
3. Gerhart J, Danilchik M, Doniach T, Roberts S, Rowning B, Stewart R: Cortical rotation of the ***Xenopus*** egg: consequences for the antero-posterior pattern of embryonic dorsal development. *Development* 1989, 107 Suppl:37–51.
4. Raible DW, Eisen JS: Lateral specification of cell fate during vertebrate development. *Curr Opin Genet Devel* 1995, 5:444–449.

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Introns

The agony column

If you have a problem, no matter how large or small, Current Biology*'s 'agony aunt' Amber can help.*

Dear Amber,
I am a *Drosophila* geneticist by training and I have been intrigued by the fuss about *Sonic hedgehog*. As a result, I made the terrible mistake of introducing my three-year-old nephew to the cartoon of the same name. Now he's addicted to a Sonic the Hedgehog video game, which has the kind of tune you simply can't get out of your head. My sister (his mother) isn't speaking to me. What should I do?

Desperate, Tübingen, Germany.

Dear Desperate,
Don't panic, you are not alone. Many scientists have had problems of this kind. There is now an on-line help group for you, at http://www.demented.com. There you will find reviews of the best earplugs and a petition to the manufacturers of Sonic the Hedgehog game asking them to provide a version in which the sound stops after 10 minutes.

Amber

Dear Amber,
I've lost my enthusiasm for the lab. I'm just not paying enough attention — some of my graduate students have been around for 10 years. Is there anything you can suggest to re-awaken my ambitious, intense, previous self?

Hopeless, Cambridge, USA.

Dear Hopeless,
No. In any case, I'm pretty sure I wouldn't want to. Why not retire and leave your space for people who can use it better?

Amber

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